Dear Colleague:

Pegylated interferon plus ribavirin combination therapy is now the standard of care for the treatment of hepatitis C virus (HCV) infection. This conclusion is based on efficacy and safety data from pivotal clinical trials and was recently affirmed in the NIH Consensus Development Conference Statement, Management of Hepatitis C: 2002. Accordingly, the majority of our HCV-infected patients can achieve a sustained virologic response with the therapies available today. Many are also experiencing favorable histologic responses.

The discussions contained within this Tx Reporter will show you how to take advantage of today’s effective therapies, as well as strategies to optimize response in your patients. For example, the enhanced efficacy of pegylated interferon plus ribavirin can be boosted further by refining treatment protocols, such as the use of weight-based dosing and adherence strategies. Treatment can be tailored to achieve the best possible outcome, in terms of virologic and histologic response, in patients with multiple challenges, patients with fibrosis and cirrhosis, and previous nonresponders and relapers. HCV RNA levels can be used to predict response to therapy as early as 12 weeks, helping you and your patients make timely treatment decisions. Additionally, an understanding of the clinical implications of pegylation and the differences between the currently available peginterferon products will inform your treatment selection.

We are pleased to bring you this issue of the Tx Reporter, Advances in Treatment of Hepatitis C: Making Clinical Sense of New and Emerging Data. I hope that you will find the critical information you need to carry out optimal treatment regimens for all your HCV-infected patients.

Sincerely,

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Learning Objectives
This activity is designed for gastroenterologists with a fundamental clinical understanding of assessment, diagnosis, treatment, and ongoing management of patients with HCV. After participating in this activity, the physician should be able to:

• Describe the efficacy and safety implications of the pharmacodynamic and pharmacokinetic properties of pegylated interferons.
• Discuss new data regarding the effect of weight-based dosing of ribavirin and treatment duration on treatment safety and efficacy.
• Evaluate the potential of early HCV RNA levels to predict response or nonresponse and the usefulness of such predictions in making early treatment-stopping decisions.
• Prescribe peginterferon/ribavirin combination therapy for all patient groups, including patients with multiple challenges.
• Relate the histologic benefit of peginterferon/ribavirin combination therapy to the need of patients with fibrosis, including those with cirrhosis.
Revisiting Critical Decision Points: Clinical Implications of 12-week Data

GARY L. DAVIS, MD

Interferon-based regimens are highly effective for treatment of chronic hepatitis C virus (HCV), with the current standard regimen of pegylated interferon and ribavirin eradicating virus in more than half of cases.¹⁻² There are challenges associated with this regimen, however, in that the regimen is complicated, uses two drugs administered by different routes, has a duration of 6 to 12 months, requires frequent monitoring, usually causes side effects, and is expensive. In addition, more than 40% of treated patients will not eradicate hepatitis C, despite a full course of therapy. Thus, assessing early virologic response (EVR) and using such an assessment to determine whether to stop or continue therapy might avoid morbidity associated with therapy, as well as the expense of unnecessary therapy in patients who will not respond. At the same time, continuation of therapy would be allowed in patients who have a reasonably high chance of achieving sustained virologic response (SVR).³ To assess EVR, the National Institutes of Health Consensus Development Conference Statement, Management of Hepatitis C: 2002 recommends quantitative HCV RNA testing.⁴

Rationale for Assessing Early Virologic Response (EVR)

The rationale for assessing EVR is based on the kinetics of hepatitis C following interferon administration. Hepatitis C replication generates 10⁸ to 10¹⁰ viral particles per day. Once treatment is initiated, these particles have a serum half-life of only a few hours. In fact, the potent antiviral effect of pegylated interferon on such rapid replication results in a rapid initial drop in HCV RNA level within the first 24 hours (Figure 1).⁴⁻⁵ The degree of this initial drop, or Phase 1, correlates with the interferon dose, as well as the viral genotype. It does not, however, correlate with SVR. Phase 1 is followed by a slower decay of the virus, or Phase 2 (Figure 1). The slope of this prolonged, and more variable, second phase of viral decay correlates very closely with SVR, with less correlation to dose and genotype.⁴⁻⁵ This close association suggests that the change in HCV RNA levels from baseline during the first weeks of therapy might predict eradication of HCV, and subsequently, response to treatment.

EVR Defined

To be clinically useful, EVR must be defined in terms of a specific drop in HCV RNA level at a specific time point in therapy. The specific drop and time point must allow two goals to be accomplished: 1) Minimize loss of continued therapy in potential sustained virologic responders, and 2) maximize stopping of therapy in nonresponders.

EVR in Standard Interferon-Based Therapy

Early studies of standard interferon monotherapy showed that failure to lose HCV RNA at 12 weeks of treatment, as measured by qualitative PCR testing, was
strongly associated with treatment failure in both 6- and 12-month regimens. Conversely, all patients who ultimately achieved SVR showed loss of HCV RNA at 12 weeks. Patients on standard interferon monotherapy, therefore, who had persistent viremia beyond 12 weeks could have discontinued therapy, without sacrificing potential SVR.

The validity of the 12-week time point for assessing EVR did not hold true in studies of interferon/ribavirin combination therapy. Instead, late responders necessitated waiting until 24 weeks to assess response. Some small and anecdotal reports, however, which used quantitative tests not widely available at that time, suggested that response might be predicted much earlier in the course with quantitative testing.

**EVR in Pegylated Interferon-Based Therapy**

Davis et al. retrospectively studied the association between early response and treatment failure using data from the 964 patients who were treated with pegylated interferon alfa-2b 1.5 µg/kg QW plus ribavirin 800 mg/d for 48 weeks in the phase 3 clinical trial by Manns et al. (n = 511) or pegylated interferon alfa-2a 180 µg QW plus ribavirin 1000 to 1200 mg/d for 48 weeks in the phase 3 clinical trial by Fried et al. (n = 453). Quantitative HCV RNA levels, measured at weeks 4, 12, and 24 of treatment, were compared with baseline level. The HCV RNA assay used was the NGI assay (Manns study) or the Roche Cobas Amplicor HCV Monitor 2.0 (Fried study) using appropriate dilutions. These methods provide a dynamic range of approximately 10⁶ to 10⁹ copies/mL, wide enough to allow assessment of quantitative changes.

The objective was to define EVR in a patient population receiving peginterferon/ribavirin combination therapy such that it optimized capture of potential responders (Goal 1), while excluding the largest proportion of nonresponders (Goal 2). The effect on cost reduction was also evaluated.

**Achievement of Goal 1: Optimized Capture of Responders**

The best definition of EVR in terms of capturing all responders was a 2-log drop in HCV RNA from baseline or PCR negativity after 12 weeks of treatment (Figure 2). Eighty-one percent (778/964) of patients achieved this. If treatment had been discontinued in the remaining 19% of patients, only 0.6% (3/529) of all sustained viral responders would have been lost by premature termination of treatment. Furthermore, more than 98% (183/186) of those who failed to reach EVR were nonresponders 24 weeks after completing a full course of treatment. In other words, <1% of sustained virologic responders are missed if using the definition of EVR as a 2-log drop at 12 weeks.

In subgroup analysis, a 2-log drop in HCV RNA or PCR negativity at week 12 was the optimal definition of EVR regardless of viral genotype, although almost all patients with genotype 2 and 3 infection achieved EVR (96% versus 73% for genotype 1). Patients who had genotype 1 infection, high HCV RNA levels, low serum ALT levels and poor adherence in the first 3 months were less likely to achieve EVR. Among the patients treated in the Manns study, the same definition of EVR was also optimal for patients who received ribavirin doses >10.6 mg/kg/d and patients who received standard interferon and ribavirin.

**Achievement of Goal 2: Exclusion of Nonresponders**

This same definition of EVR (a 2-log drop in HCV RNA from baseline or PCR negativity at 12 weeks) was also the best in terms of excluding the largest proportion of nonresponders (Figure 3). Nineteen percent of patients did not achieve EVR using this definition. Of these 186 patients, almost all remained treatment failures (negative predictive value = 0.98) and only 3 (1.6%) achieved SVR after completing the next 9 months of therapy. Thus, failure to achieve EVR is an accurate marker for nonresponse to a full course of therapy and can be used to prompt discontinuation of treatment without denying treatment to patients who have a reasonable chance of a viral response.

**Cost Reduction**

Continuing therapy only in patients likely to respond, while discontinuing it in patients unlikely to respond will reduce costs associated with therapy. Cost reductions were estimated by Davis from the same database using hypothetical scenarios involving various definitions of EVR (Table 1). For example, if treatment were stopped in patients who were PCR negative at 4 weeks, the estimated cost

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**Table 1. Early Virologic Response: Percent Stopping Therapy for Lack of EVR**

Reprinted from Hepatology, 36, Davis GL, Monitoring of viral levels during therapy of hepatitis C, S146-S151, Copyright 2002, with permission from Elsevier.
reduction is 59%. Seventy-two percent of patients, however, would have stopped therapy, with a loss of 56% of responders. In contrast, if treatment were stopped in patients with a 2-log drop in HCV RNA level at 12 weeks, 19% of patients would have stopped therapy, with a loss of only 0.6% of responders for both time points. Cost reduction is estimated at 16%.

**Failure to Achieve SVR with EVR**

Of those patients who did reach an EVR, defined as a ≥2-log drop or PCR negativity at 12 weeks, only 68% went on to achieve SVR. Several reasons have been suggested as to why this percentage is not higher: residual viremia, poor treatment adherence, and genotype 1 infection. The majority of early virologic respondents (89%) are PCR negative at 12 weeks. Eighty percent of these go on to achieve SVR. Of those who remain PCR positive at 12 weeks, despite a 2-log drop, only 20% achieve SVR. Of this latter subset who remain PCR positive at 12 weeks, those who subsequently lose detectable virus before 24 weeks have about a 50% chance of SVR while those who still remain PCR positive do not respond. Adherence in the first 12 weeks of therapy is critically important. Patients who receive ≥80% of peginterferon and ≥80% of ribavirin doses for ≥80% of the time during the first 12 weeks have nearly an 80% chance of achieving EVR (Schering-Plough Research Institute, data on file). A reduction of interferon to less than 80% of the total prescribed dose during this period reduces the chance of SVR to 53%. Likewise, a reduction of ribavirin to less than 80% of the prescribed dose reduces the chance of EVR to 35%. Reductions of either drug after 12 weeks (<80% prescribed dose) have much less impact of subsequent treatment response, although prolonged interruptions or complete discontinuation of therapy after EVR reduces the chance of SVR to 50%.

EVR is best defined as a ≥2-log drop or PCR negativity at 12 weeks, regardless of genotype. Nevertheless, fewer patients with genotype 1 infection achieve EVR compared with patients with genotype 2 or 3 infection, 73% versus 96%, respectively. The positive predictive value (ie, the chance of achieving SVR after EVR) in genotype 1 infection is 60% compared with 85% in genotype 2. The negative predictive value (ie, the chance of not achieving SVR without EVR) is very low in all genotypes.

**Practical Guidelines**

These data justify the following practical guidelines in managing combination therapy with interferon and ribavirin in patients with hepatitis C. These guidelines apply whether using pegylated or standard interferon, or pegylated interferon alfa-2a or alfa-2b.

- **EVR** is defined as a ≥2-log drop in HCV RNA or PCR negativity at 12 weeks. Patients who do not achieve EVR are not likely to achieve SVR, and therefore should discontinue combination therapy.
- **Patients who do achieve EVR, yet remain virus positive at 12 weeks, should be retested at 24 weeks. If virus is still present at that time, combination therapy should be stopped.**
- **Physicians and patients must make every effort to ensure good adherence (≥80% of peginterferon and ribavirin doses for ≥80% of the time), particularly during the first 12 weeks.**
- **HCV RNA testing during therapy may not be cost effective for patients infected with genotypes 2 or 3, as EVR is so common among this population. However, HCV RNA testing 6 months after completion of treatment to assess SVR is still recommended.**
- **Although viral assays are accurate and reproducible, the results from different assay methods are not interchangeable. The same viral assay must be used at baseline and throughout therapy.**

Consideration of these recommendations also requires recognition of the potential, yet unproven, histologic benefits of treatment in nonresponders. Although the principle of stopping therapy based on EVR assumes that SVR is the only beneficial endpoint of treatment, some patients treated with interferon achieve histologic improvement during therapy, despite not clearing virus. Whether such improvement is sustained or has any impact on the natural history of the disease remains to be demonstrated and is currently being assessed in prospective studies.

**Conclusion**

Assessing EVR is helpful in the treatment of patients with chronic hepatitis C who receive interferon-based combination therapy. It can provide patients and treating physicians with an early goal and motivate them to adhere to treatment recommendations. Discontinuation of therapy in the minority who fail to achieve EVR reduces treatment costs and avoids the potential morbidity associated with therapy in those with no chance of viral clearance.
IRA M. JACOBSON, MD

Two pegylated interferons are currently approved for the treatment of chronic hepatitis C. Peginterferon alfa-2b was approved in January 2001 for treatment as monotherapy, and in August 2001, for treatment in combination with ribavirin. Peginterferon alfa-2a was approved more recently, in October 2002, for treatment as monotherapy, and in December 2002, for treatment in combination with ribavirin.

What is Pegylation?
Pegylation is the binding of inert polyethylene glycol (PEG) to drug products, including, but not limited to, protein pharmaceuticals. Pegylation is a well-known technology, and a number of other pegylated protein products are in clinical use or development, including pegademase (pegylated adenosine deaminase) for treatment of severe combined immunodeficiency, pegasparagase (pegylated L-asparaginase) for the treatment of acute lymphoblastic leukemia, pegfilgrastim (pegylated granulocyte colony-stimulating factor) for the treatment of neutropenia, and pegvisomant (pegylated growth hormone receptor antagonist) for the treatment of acromegaly.

PEG has several advantages as a drug-modifying agent:
- It is inert, having no activity of its own within the body.
- It is water soluble.
- It can be “custom designed” as linear or branched, and made any size by varying the number of hydroxyethylene groups.

Rationale for Pegylation of Protein Pharmaceuticals
Several factors limit the therapeutic utility of protein pharmaceuticals. Many protein pharmaceuticals have short half-lives because they are quickly cleared from the body. In addition, they may be degrades through proteolytic processes within the body. Immunogenicity is another concern, as protein pharmaceuticals can induce an antibody response.

Pegylation offers advantages related to these limitations. Pegylation decreases drug clearance, thereby prolonging the half-life and resulting in more sustained blood levels and the added convenience of less frequent administration. In addition, it is expected to decrease proteolysis and immunogenicity of the protein pharmaceutical.

Pegylation of Interferon
Pegylation of interferon alfa-2a and alfa-2b for the treatment of hepatitis C is desirable because the standard interferons have plasma half-lives of only 3 to 8 hours and are virtually undetectable after 24 hours (Figure 4). Of particular significance is the viral re-emergence during the nadir period, when the drug essentially becomes undetectable. Viral kinetic studies have demonstrated that maximum suppression of HCV replication is not maintained during the traditional 48- to 72-hour dosing cycle of standard interferons.

Pegylation of interferon results in more sustained exposure to interferon with a much greater area under the curve.

The Two Pegylated Interferons
The peginterferon alfa-2a molecule consists of interferon alfa-2a and a 40-kD branched PEG moiety, consisting of two 20-kD branches (Figure 5). This PEG is attached via a lysine-lysine bond to primarily one of four lysine residues on the interferon alfa-2a molecule. In contrast, the peginterferon alfa-2b molecule consists of interferon alfa-2b and a single 12-kD straight-chain PEG moiety. Approximately 50% of this PEG is bound to histidine residues at the 34th amino acid location on the interferon alfa-2b molecule, and the remainder to one of several lysine residues.

The benefits of both peginterferons have been demonstrated repeatedly in clinical trials. Studies of the pegylated interferons given as monotherapy demonstrated a twofold increase in the rate of SVR compared with the respective standard interferons, thereby confirming that theoretic pharmacokinetic concepts can be translated into greater efficacy and convenience to the patient with once-
versus thrice-weekly parenteral drug administration. The recent trials of Manns et al. and Fried et al. further confirmed the superiority of pegylated interferons combined with ribavirin versus standard interferon plus ribavirin.

An inverse correlation between treatment efficacy and body weight, or body surface area, has been observed with standard, fixed dosing of interferons as monotherapy or in combination with ribavirin. To equalize efficacy across all patients regardless of body weight, peginterferon alfa-2b was designed to be dosed by body weight, currently at 1.5 µg/kg when used in combination with ribavirin. In contrast, peginterferon alfa-2a has been developed as a fixed-dose product, with 180 µg emerging from early dose-ranging trials as the favored dose.

Pharmacokinetics and Biologic Activity of Peginterferons

The pharmacokinetics and biologic activity of pegylated interferons are affected by the physical features of pegylated pharmaceuticals, such as molecular weight, size, structure, and conjugation site.

Serum Concentration

The pharmacokinetics of the two peginterferon products, in terms of serum concentration, vary considerably (Table 2). Peginterferon alfa-2b is absorbed and achieves maximum concentration more quickly than peginterferon alfa-2a. Peginterferon alfa-2a, however, has a more sustained period of maximum concentration. The elimination half-life of peginterferon alfa-2a is about twice as long as that of peginterferon alfa-2b, and trough levels at 48 weeks are much higher for peginterferon alfa-2a than peginterferon alfa-2b. Whether the different rates of clearance of the two peginterferons might be clinically significant under any circumstances of drug toxicity remains to be evaluated as experience accumulates.

Pharmacokinetic studies demonstrate that peginterferon alfa-2a has a peak-to-trough ratio of 1.5 to 2:1, while that for peginterferon alfa-2b is 6:1. Importantly, the area under the curve of peginterferon alfa-2b 1.5 µg/kg is about 50 times greater than that of standard interferon alfa-2b. Peginterferon alfa-2a at the fixed dose of 180 µg has an even greater area under the curve. Despite the pharmacokinetic differences between peginterferon alfa-2b and alfa-2a, however, trough blood levels at week 4 for peginterferon alfa-2b 1.5 µg/kg/wk are similar to peak blood values obtained when standard interferon alfa-2b is used. This is consistent with a once-per-week drug.

In support of this, Lurie et al. showed that peginterferon alfa-2b 1.5 µg/kg administered twice per week resulted in no higher a viral load reduction at week 12 compared with peginterferon alfa-2b 1.5 µg/kg administered once per week, 50% versus 70%, respectively.

The volume of distribution is considerably greater for peginterferon alfa-2b than peginterferon alfa-2a (Table 2). This lesser volume of distribution has been invoked as an argument to support fixed, rather than weight-based, dosing. However, the landmark trials of peginterferon alfa-2a monotherapy by Zeuzem et al. and peginterferon alfa-2a in combination with ribavirin by Fried et al. demonstrated that body surface area and body weight, respectively, were significant variables associated with the likelihood of sustained response.

Renal Clearance

Both peginterferon products are metabolized primarily in the liver, but the difference in weight and size of the two peginterferons results in differences in renal clearance. Distribution and tissue uptake studies in mice demonstrated that renal clearance is inversely related to PEG molecular weight, decreasing with increasing PEG molecular weight and increasing with decreasing PEG molecular weight. These conclusions have been supported and expanded by a model of PEG bound to dextran-bound phenylalanine, which demonstrates how PEG size affects renal clearance. The 12-kD PEG-dextran in this model has a Stokes radius of 38Å. According to this model, it can be postulated that the smaller peginterferon alfa-2b has about 30% renal clearance, with virtually no renal clearance for the larger peginterferon alfa-2a. Indeed, an abstract by Modi et al. suggested that in rats most of the peginterferon alfa-2a is metabolized by the liver. Counter to these theoretic considerations of PEG size and renal excretion, however, exposure to peginterferon alfa-2a is found to be increased by about 25% to 45% in patients with end-stage renal disease who are on hemodialysis. Furthermore, both product manufacturers advise their respective products be used with caution in patients with creatinine clearance <50 mL/min.

Bioactivity

In general, pegylation is expected to result in a loss of specific bioactivity of protein pharmaceuticals. The differences in sustained exposures of the two peginterferons must be assessed within the context of potential differences in bioactivity of these two interferon molecules, which are bound to different PEG molecules. The size of the PEG molecule affects...
not only clearance, but also may affect the specific activity of the resultant peginterferon product. A larger PEG molecule may potentially result in greater steric hindrance by affecting the ability of the active site of the interferon molecule to bind with its receptor. A larger PEG molecule, therefore, may result in a greater loss of activity.

In a study by Grace et al., the specific activity of peginterferon alfa-2b was assessed relative to standard interferon alfa-2b, as measured by protein concentration needed to provide 50% antiviral protection. (Standard interferon alfa-2b was considered the standard, with a specific activity of 100% by definition.) It was found that the specific activity of peginterferon alfa-2b was 28% relative to standard interferon alfa-2b. It is apparent from these data that some specific activity is lost by the pegylation of interferon, as expected. More peginterferon is needed, in terms of pg/mL of interferon protein, to achieve the same degree of antiviral protection as standard interferon. A study by Bailon et al. also demonstrated the drop in specific activity with pegylation. In a model of bovine kidney cells challenged with VSV, peginterferon alfa-2a had an antiviral specific activity of 7% relative to interferon alfa-2a.

Antiproliferative activity in a variety of malignant cell lines also demonstrate differences between the two products, with lower activity observed with peginterferon alfa-2a relative to peginterferon alfa-2b. In addition, STAT activation, an interferon-induced intracellular signaling event, is comparably less with peginterferon alfa-2a than with peginterferon alfa-2b, at equivalent weight dosing. STAT activation is part of the JAK/STAT pathway, which helps to turn on genes that are responsive to interferon.

The amino acid residue on the interferon molecule to which PEG is bound also affects specific activity. Binding to histidine has been associated with approximately fourfold greater preservation of specific activity in comparison to binding to lysin. Again, if the specific activity of standard interferon is 100%, by definition, the specific activity of PEG molecules bound to His34 residues on interferon is 37%, and 9% for PEG molecules bound to Lys121 residues. The finding of a specific activity of 28% for peginterferon alfa-2b by Grace et al. is consistent with a product having about 50% of its PEG molecules bound to histidine residues (Figure 6). The relative contributions of PEG size and histidine conjugation to the difference in specific activity of the two peginterferons is unclear.

In vivo clinical significance, however, cannot be directly extrapolated from these in vitro data. Although a larger PEG molecule may be associated with a lower in vitro specific activity, it may not be associated with less clinical efficacy in vivo. The lower specific activity may be offset by other factors. In fact, the prolonged half-life of a larger PEG is a greater determinant of bioactivity in vivo than would be expected from in vitro data. Experimental data support this contention by demonstrating a direct correlation between PEG mass and activity in vivo, unlike the inverse correlation of PEG size and specific activity observed in vitro. The use of a PEG molecule that has low specific activity may warrant the administration of a greater amount of interferon protein. This is exemplified by the peginterferon alfa-2a product, which is given with a larger fixed dose of 180 µg compared with peginterferon alfa-2b, which is given in a calculated dose based on weight (1.5 µg/kg).

Conclusions

The two available peginterferon products confer enhanced therapeutic efficacy when compared with their standard interferon counterparts. Both have the added convenience of once-weekly dosing with no novel toxicities. In addition, both products in combination with ribavirin allow the clinician to predict the likelihood of SVR and to determine the potential for stopping therapy at 12 weeks, earlier than the 24 weeks required by standard interferon plus ribavirin therapy. Given the very close similarities in therapeutic efficacy of peginterferons alfa-2b and alfa-2a in the major trials, there appears to be no rationale for beginning treatment with one product after failure to respond to the other product.

A key clinical area of difference is in the dosing of the two products, with peginterferon alfa-2b weight-based dosed and peginterferon alfa-2a flat dosed. Further study is needed in this area, as the major pegylated alfa-2a trials did find significant differences in outcome based on body surface area with monotherapy and body weight with combination therapy. It is unclear how important are the differences in clearance between the two peginterferon products. A recent abstract suggested that peginterferon alfa-2a is expected to take about 4 to 8 weeks to clear compared with 10 to 14 days for peginterferon alfa-2b. It is also unclear how the differences in PEG size and specific activity result in clinically significant differences in outcome. Any significance of these differences may become evident only as additional experience accumulates with the use of the newer product.
Treating the Patient with Multiple Challenges

JOHN G. McHUTCHISON, MD

Case Presentation
An obese, 46-year-old male stockbroker presented for evaluation of incidentally detected hepatitis C virus (HCV) infection. Recently relocated from Houston, this motivated gentleman was starting a business and had a young family. Apart from a lifelong struggle with weight, he had no significant health history. Several years ago, he reported having noncardiac chest pain, but subsequent cardiac evaluation was unremarkable.

His evaluation included elevated liver enzymes (AST, 290 U/L; ALT, 385 U/L), normal complete blood count and hepatic synthetic function (albumin, bilirubin, and prothrombin time), HCV genotype 1 infection, and high viral load (1.1 million IU/mL). Due to his weight (325 lb), the liver could not be visualized during ultrasound. Liver biopsy revealed moderate inflammation and steatosis, as well as bridging fibrosis. On the basis of this result, it was difficult to differentiate how much of the patient’s liver disease was due to hepatitis C versus nonalcoholic fatty liver disease, perhaps nonalcoholic steatohepatitis.

The patient had no contraindications to therapy. Therefore, after discussing his situation and the results of his liver biopsy, it was decided that he begin therapy with a weight-based dosing regimen of peginterferon alfa-2b 1.5 µg/kg and ribavirin 1400 mg/d. At 12 weeks, he had a significant reduction in viral load (to 15,000 IU/mL), some reduction in his liver enzymes (AST, 100 U/L; ALT, 45 U/L), and expected, but tolerable, side effects including rash, insomnia, and weight loss. His hemoglobin level dropped from 16 g/dL to 13 g/dL, as is common in patients taking ribavirin. Because the reduction in HCV RNA was slightly less than a 2-log reduction, viral load testing was repeated at week 14, and a 2-log reduction in HCV RNA was confirmed. At week 20, the patient reported depression and was started on an antidepressant.

The patient continued on therapy, and repeat testing at week 24 revealed no detectable serum HCV RNA. He successfully completed 48 weeks of therapy and serum HCV RNA was undetectable at that time. His ALT level remained elevated (85 U/L), presumably from persistent steatosis. He remained HCV RNA negative 3-months posttreatment, and currently awaits his 6-month follow-up visit to determine if he has achieved an SVR.

Adherence and its importance was discussed and recorded at each monthly visit during therapy. He received 90% of the prescribed medication dosages.

Discussion: Treatment in Practice
This patient may be considered hard to treat due to the presence of a number of factors predictive of poor response: obesity, genotype 1 infection, high viral load, bridging fibrosis, >40 years of age, and male gender. Yet he achieved a good outcome as a result of a careful, individualized treatment plan and his own motivation to adhere to that plan.

Decision to Treat
Of this patient’s negative predictive factors, particularly significant were obesity, genotype 1 infection and high viral load. Data from the phase 3 clinical trials of both peginterferon alfa-2b and peginterferon alfa-2a in combination with ribavirin show that patients infected with genotype 1 have a lower overall SVR rate. Genotype 1 infection plus high viral load confer an even lower SVR rate. Neither of these studies, however, was powered or designed to statistically address the issue of the effectiveness of the drug specifically in the subgroup of patients with genotype 1 infection and high viral load.

This patient’s negative predictive factors must be balanced against the fact that his liver disease had the potential to accelerate over the next 5 to 7 years and develop into cirrhosis. The presence of bridging fibrosis and steatosis placed him at significant risk for this progression. Bridging fibrosis is certainly a risk factor for cirrhosis, and the bulk of evidence suggests that steatosis itself contributes to fibrosis.35

The patient’s noncardiac chest pain was not a contraindication to therapy, provided cardiac evaluation by a cardiologist was unremarkable.

Weight-Based Therapy
A weight-based dosing regimen of both peginterferon and ribavirin demonstrated efficacy for this patient despite the presence of negative predictive factors: higher weight and genotype 1 infection. Peginterferon alfa-2b is designed to be a weight-based product, with an optimal dosage of 1.5 µg/kg, in order to equalize efficacy across all patients regardless of body weight. In addition, weight-based dosing of ribavirin has been shown to result in enhanced response rates in patients with genotype 1 infection.1

In the phase 3 clinical trial of peginterferon alfa-2b plus ribavirin conducted by Manns et al.,1.5 µg/kg peginterferon was paired with 800 mg ribavirin. Although these became the FDA-approved doses of both products, categorical analysis of data from this trial indicated that SVR rates were significantly related to the dose of ribavirin on a mg/kg basis, with the optimal dose of ribavirin identified as 13 ± 2 mg/kg/d.

Figure 7. Peginterferon Plus Ribavirin: Genotype 1

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<th>Dosage</th>
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Patients with genotype 1 infection who received >10.6 mg/kg/d ribavirin had an enhanced SVR rate of 48% compared with 42% in patients who received a flat dose of 800 mg/d (Figure 7). For all genotypes combined, patients who received ≥10.6 mg/kg/d ribavirin also achieved enhanced SVR rates compared with patients who received a flat dose of 800 mg/d: 61% and 54%, respectively. In the phase 3 clinical trial of peginterferon alfa-2a 180 µg plus ribavirin 1000 to 1200 mg/d conducted by Fried et al, the SVR for patients with genotype 1 infection was 46%.

This patient received 1400 mg/d ribavirin, due to his weight of 325 lb. Early data from an ongoing trial by Jacobson et al show that this dose of ribavirin appears safe and causes no greater degree of hemolytic anemia than lower doses of ribavirin in patients of comparably lower weight. Caution is in order, however, in any patient with a history of risk factors.

to achieve SVR, this viral load result represented a decision point for the physician and patient: should treatment be stopped or continued?

Three caveats related to viral load assays should be taken into consideration when judging the significance of a 12-week viral load assay result. First, in order to compare baseline and 12-week HCV RNA levels, the results must be comparable in terms of units. Comparison of interassay quantitative values for HCV RNA tests have now been facilitated by the introduction of international standard units (IU), the new “gold” standard for reporting HCV RNA levels. Although assays that report in terms of IUs are considered comparable, occurrence of inter-laboratory variation in assays suggests that the same laboratory should be used at all time points. Second, assays are considered accurate within about a half-log.* HCV RNA levels that are around the 2-log decrease should thus be evaluated in the context of this limit of accuracy. Third, some laboratories do not dilute samples that exceed an assay’s upper limit of detection.

Taking these caveats into account, this patient’s HCV RNA level reduction was considered sufficient to justify continuing therapy. Both viral load tests—at baseline and at 12 weeks—were performed using the same assay, by the same laboratory, and were reported quantitatively. Thus, they may be compared with the same assumed degree of accuracy. Furthermore, the difference between the patient’s degree of HCV RNA level reduction and the 2-log reduction threshold approached the assay’s acceptable degree of error. As a second check, viral load testing was repeated at 14 weeks and a 2-log reduction was confirmed at this time. Despite this reduction, the patient remained virus positive and so was rechecked at 24 weeks, at which time the final decision was made about continuation for the full 48 weeks.

Adherence
Adherence was an important part of this patient’s successful treatment plan. A recently published retrospective analysis of data from the phase 3 clinical trial of peginterferon alfa-2b plus ribavirin indicated that patients with genotype 1 infection who received weight-based ribavirin >10.6 mg/kg/d and were largely adherent to the therapy protocol had a significantly higher SVR rate compared with patients who received the same dose but were less adherent: 63% versus 34% (P = .008) (Figure 8). This group was defined as those that received ≥80% of peginterferon dose plus ≥80% of ribavirin dose for ≥80% of the duration of therapy. The less adherent group received <80% of peginterferon dose and/or <80% of ribavirin dose, but for ≥80% of the duration of therapy. The overall SVR by intent-to-treat analysis for patients with genotype 1 infection at that ribavirin dose was 48%.

Conclusion
This case study illustrates that the best possible outcomes can be achieved in hard-to-treat patients through individualized treatment plans that employ strategies to optimize response (Figure 9). Such a plan includes the most effective dose of pegylated interferon, the most appropriate dose of ribavirin, evaluation of early response, a commitment to adherence on the part of the physician and patient, management of side effects by dose reduction rather than discontinuation, and ongoing patient support and education.

*Half-log.38 HCV RNA levels that are around the 2-log decrease should thus be evaluated in the context of this limit of accuracy.
Achieving Histologic Benefit

NEZAM H. AFDHAL, MD

Case Presentation

A Caucasian male, 42 years of age and weighing 205 pounds, was seen in the Liver Center. In 1993, he was diagnosed with hepatitis C virus (HCV) infection, genotype 1a, when he presented with an abnormal ALT level during an evaluation for life insurance. He admitted to using intravenous drugs on several occasions many years ago, and it is likely that this was the source of his infection. A heavy drinker from age 22 to 33 years, he has had no alcohol for the last 8 years.

In 1994, a liver biopsy demonstrated significant liver injury with grade 2 inflammation and stage 2/3 fibrosis on the METAVIR scale. He was treated initially with interferon alfa-2b 3 MIU TIW and weight-based ribavirin 1200 mg/d. He failed to respond after 6 months and therapy was stopped. He reported that he had taken the full doses throughout treatment. There was no further evaluation until his current presentation.

On presentation to the Liver Center, he complained of fatigue and occasional right upper quadrant pain. He was found to have hepatosplenomegaly, elevated transaminases, and an HCV RNA level of 4.32 million copies/mL (National Genetics Institute). His bilirubin, albumin, and International Normalized Ratio (INR) were all normal, indicating fairly good hepatic synthetic and excretory function. Of note, his platelet count was relatively low at 68,000/mm³. His alpha-fetoprotein (AFP) was elevated at 23 ng/mL (normal <7 ng/mL). Despite the elevated AFP, an ultrasound confirmed hepatosplenomegaly without any focal mass or ascites. A liver biopsy showed well-established cirrhosis, stage 4, grade 2 (METAVIR). An upper-GI endoscopy showed the presence of portal hypertension as evidenced by small esophageal varices.

The potential for response with retreatment was discussed with the patient and the decision was made to start him on a weight-based treatment regimen of peginterferon alfa-2b 1.5 µg/kg QW and ribavirin 1200 mg/day. The patient was adherent and tolerated treatment well, with no dose reductions.

At week 12, his viral load had dropped to 1.3 million copies/mL, and at week 24, to 810,000 copies/mL, considerably less than a 2-log response. This degree of response indicated that he would not achieve SVR even with a full course of therapy.

With the primary goal of viral eradication not achieved, the secondary goals of preventing disease progression and decreasing the risk of hepatocellular carcinoma (HCC) were discussed with the patient. The patient elected to enroll in a maintenance therapy clinical trial (COPILOT), in which the efficacy of interferon as an antifibrotic, rather than as an antiviral, agent is studied. He was randomized to receive peginterferon alfa-2b 0.5 µg/kg QW. He tolerated this well, with occasional mild thrombocytopenia down to 30,000/mm³. (Note: The patient began therapy with relatively low platelets and was now without the protective effects of ribavirin.) The thrombocytopenia resolved after cessation of peginterferon for a week.

By week 48 of maintenance therapy, the patient’s ALT level had dropped to 56 U/L and his HCV RNA level was 610,000 copies/mL. At week 96, ALT and HCV RNA levels were both below baseline, 72 U/L and 410,000 copies/mL, respectively. More importantly, an endoscopy showed no evidence of varices or portal hypertensive gastropathy, and a liver biopsy showed a reduction in grade of inflammation, from an Ishak 6 to an Ishak 4.

Discussion: Treatment in Practice

The current approach to the patient who has histologic and clinical progression of liver disease, particularly one who has failed standard interferon/ribavirin therapy, is complex. Treatment decisions require both individualization and an understanding of the secondary goals of therapy, which are to prevent disease progression and decrease the risk of HCC.

Decision to Re-treat

The patient with cirrhosis is at great risk for developing decompensated cirrhosis.40 Every effort should be made to provide these patients with the opportunity for efficacious treatment, despite the presence of negative predictive factors. Retreatment not only offers another chance at viral eradication, but also at histologic improvement. This potential benefit is a strong factor in favor of re-treating patients who have established cirrhosis or bridging fibrosis, despite the lack of mature data on retreatment response rates in this population.

In this case, the patient was interested in retreatment due to the significant
progression of his liver disease in the years since he was last evaluated. He wanted to know, however, what therapeutic advances had occurred during that interval that might give him a chance at response. After all, he had been a true nonresponder. He had taken his prescribed regimen of both drugs for 6 months before stopping therapy, yet he had not significantly responded.

The availability of pegylated interferon in combination with ribavirin, and its improved efficacy over standard interferon in combination with ribavirin was discussed with him as a significant advance. Another advance was the option of weight-based dosing. His past treatment of standard interferon plus ribavirin included a flat dose of interferon alfa-2b. With flat-dosed interferon alfa-2b, body surface area (BSA) has been shown to be a significant predictive factor for SVR (Figure 10). (Schering-Plough Research Institute, data on file), ie, the larger the BSA, the less likely is SVR. Retreatment with weight-based dosing of peginterferon alfa-2b allows treatment to be tailored according to a person’s body weight, thereby negating the effect of BSA on treatment response (Figure 11). The higher efficacy of pegylated interferon, together with the ability to individualize therapy with weight-based dosing, may provide a greater likelihood of response in a patient with negative predictive factors (genotype 1 infection, high viral load, advanced fibrosis with bridging, and a large BSA).

![Figure 12. Fibrosis Score and Cirrhosis](image)


The rate of progression to cirrhosis can be estimated from the degree of fibrosis on initial liver biopsy, with increased rates associated with more severe fibrosis. Yano et al studied 70 HCV-infected patients. Each of the study patients had undergone 2 to 10 liver biopsies (mean, 3.9) over an interval of 1 to 26 years (mean, 8.8 years). The biopsy scores were correlated with progression of disease, if any, and transition to cirrhosis. All patients with stage 3.0 to 3.4 liver disease in the initial biopsy progressed to unequivocal cirrhosis by 10 years. Approximately 35% of patients who initially presented with stage 2.0 to 2.9 liver disease progressed to cirrhosis within 5 years (Figure 12). This finding is consistent with the clinical history of this patient. His disease progressed from stage 2/3 to stage 4 over a period of about 5 years.

Treatment with interferon-based regimens has been shown to improve fibrosis stage in a significant proportion of patients. Poynard et al used pooled data from 3010 patients with paired liver biopsies from four randomized trials of standard interferon alfa-2b (as monotherapy and in combination with ribavirin), and pegylated interferon alfa-2b (as monotherapy and in combination with ribavirin), comprising a total of 10 different treatment regimens. For all treatment regimens, 12% to 24% of patients achieved improvement in fibrosis stage, even with a treatment period as short as 1 year (Figure 13). Twenty-four percent of patients receiving peginterferon alfa-2b 1.5 μg/kg plus ribavirin >10.6 mg/kg/d improved by at least one fibrosis stage, 68% remained stable, while fibrosis worsened in only 8%. Necrosis and inflammation improvement were found in 73% of patients receiving peginterferon alfa-2b 1.5 μg/kg plus ribavirin >10.6 mg/kg/d. All regimens significantly reduced the fibrosis progression rates in comparison to rates before treatment. Furthermore, cirrhosis was reversed in 49% (75/153) of cirrhotic patients. Only one-third of patients with cirrhosis reversal were sustained responders.

This study demonstrated the positive impact of treatment on fibrosis as the major rationale for long-term therapy, or maintenance therapy, in patients with fibrosis or cirrhosis who have not responded virologically to peginterferon plus ribavirin. Unlike primary therapy, the focus of maintenance therapy is not on virologic response, but on the prevention of liver disease and HCC. Within this context, it appears that, as an antifibrotic, interferon may be as efficacious alone as in combination with ribavirin, and so maintenance therapy regimens typically do not include ribavirin.

**Decision to Begin Maintenance Therapy**

Upon retreatment, the patient again did not achieve a virologic response. The less than significant viral load reduction at 12 and 24 weeks indicated an absence of EVR, which has been demonstrated to be predictive of nonresponse in treatment-naive patients on primary therapy, as well as in nonresponders on retreatment. Treatment was continued, however, through week 24 to give the patient every opportunity for response due to his individual negative predictive factors and cirrhosis.

It was evident that this patient was not going to be cured of his HCV infection with ongoing primary therapy. The focus of treatment, therefore, shifted to retarding the progression of his liver disease or even improving his fibrosis with a long-term course of pegylated interferon monotherapy for maintenance.
**Maintenance Therapy Clinical Trials**

Several studies on maintenance therapy are being undertaken both nationally and internationally. They include COPILOT (Colchicine vs PegIntron® Long-Term), sponsored by Schering Hepatitis Innovations; HALT-C (Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis), sponsored by the National Institutes of Health; EPIC-3 (Evaluation of PegIntron in Control of Hepatitis C Cirrhosis), also sponsored by Schering Hepatitis Innovations; and AEGIS (AntiFibrotic Efficacy Gamma Interferon Study), sponsored by InterMune Inc.

In COPILOT, nonresponders to interferon/ribavirin or peginterferon/ribavirin with an Ishak fibrosis score >3 are randomized to receive either colchicine 0.6 mg BID or peginterferon alfa-2b 0.5 µg/kg QW. Primary endpoints include death or transplant, variceal bleed, increase in Child-Pugh-Turcotte score >2, and HCC. Secondary endpoints include histology, fibrosis markers, and quality of life. Preliminary data at 1-year follow-up show a greater number of primary endpoint clinical events in the colchicine arm (17/141) compared with the peginterferon arm (7/146).44

In addition, Kaplan-Meier survival curves demonstrate that a significant benefit is present even at this early time point for patients that have been randomized to the pegylated interferon alfa-2b maintenance arm. The study is at an early stage, however. More time is needed before these results can be validated over a longer time period.

**Conclusion**

This case study illustrates that treatment can be individualized to optimize histologic response, even in nonresponders to peginterferon plus ribavirin combination therapy. The antifibrotic benefit of interferon as part of primary therapy has been shown to improve or stabilize the progression to fibrosis. Early data from maintenance therapy clinical trials show a trend toward decreased occurrence of clinical events associated with advanced liver disease and a survival benefit in patients receiving low-dose peginterferon monotherapy as maintenance.  

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**Re-treating with Peginterferon/Ribavirin: Hope for the Nonresponder**

**IRA M. JACOBSON, MD**

**Case Presentation**

A 49-year-old Caucasian male, weighing 79.1 kg, was referred for evaluation. He had been diagnosed with hepatitis C, genotype 1b infection, in 1998. A biopsy done at that time showed stage 3, grade 3 liver disease, with moderate to severe steatohepatitis, perivenular and pericellular fibrosis, and mild necro-inflammatory activity consisting of aggregates of neutrophils, indicative of liver damage caused by nonalcoholic steatohepatitis, in addition to HCV infection. At diagnosis, his HCV RNA level was 62,000 copies/mL and ALT level was 100 U/L. Although this drop in HCV RNA level was significant, the log drop could not be determined, because the testing laboratory had not diluted the sample in order to measure the actual level at baseline. At the end of treatment, his ALT level was again >1 million copies/mL. He and his physician discussed the possibility of achieving SVR by retreatment with a regimen of peginterferon/ribavirin. The patient agreed to enroll in a retreatment study and was randomized to receive peginterferon alfa-2b 1.0 µg/kg and ribavirin 1000 to 1200 mg/d.

By week 12, he experienced a >2-log drop in HCV RNA, down to <1000 copies/mL. By week 24, HCV RNA was undetectable and remained so throughout week 72 posttreatment.

During treatment, the patient experienced common side effects of combination therapy, including fatigue, depression, anemia, and rash. He declined antidepressants and completed therapy with only a small and temporary reduction of ribavirin dose, due to anemia. He reported relief from side effects within days of completing therapy.
and felt well throughout the posttreatment follow-up period.

Discussion: Retreatment of Prior Treatment Failures

The large number of interferon/ribavirin nonresponders or relapsers may have another chance at viral eradication with pegylated interferon/ribavirin, due to the improved efficacy of pegylated interferon. A number of investigator-initiated trials have been started to study response in prior nonresponders and relapsers re-treated with peginterferon/ribavirin. These trials feature significant heterogeneity in terms of study design, particularly with regard to doses. From the data obtained thus far from these trials, it is clear that peginterferon/ribavirin can clear HCV RNA in a significant number of prior nonresponders and relapsers re-treated with peginterferon/ribavirin. This appears to be related to a lower rate of relapse after 12 months of treatment, a rate higher than reported in prior nonresponders (25%–40%) while on peginterferon/ribavirin can clear HCV RNA in a significant number of prior nonresponders and relapsers re-treated with peginterferon/ribavirin. These data affirm that true resistance does exist among patients with genotype 1 infection (n = 198) who did not respond to previous combination therapy achieved statistically higher response rates with the higher dose of peginterferon. By the end of the 24-week follow-up period, however, the percentage of patients who achieved SVR was low, with no statistical difference between the peginterferon alfa-2b 1.0 µg/kg and peginterferon alfa-2b 1.5 µg/kg groups (5% versus 9%, respectively) (Figure 14). This rate of 9% for high-dose peginterferon is similar to results seen thus far in other studies.

Nonresponders with genotype non-1 infection (n = 17) also had low rates of SVR: 25% and 13% for low- and high-dose peginterferon, respectively (P = NS). These data affirm that true resistance does exist among patients with genotype 2 or 3 infection, a group typically considered sensitive to therapy (Figure 15). Combination therapy relaxers of all genotypes (n = 49) had much better SVR rates. Fifty-four percent of those who received high-dose peginterferon achieved SVR, compared with 35% of those who received low-dose (P = NS). Interferon monotherapy nonresponders (n = 42) had relatively modest rates of SVR: 24% and 14% for low- and high-dose peginterferon, respectively (P = NS).

Several other studies on retreatment were also presented at the 53rd AASLD Annual Meeting. Krawitt et al presented data demonstrating an SVR rate of 16% in genotype-1–infected prior nonresponders and 51% in genotype-1–infected relapsers upon retreatment with peginterferon alfa-2b 100 µg (<75 kg) or 150 µg (>75 kg) QW plus ribavirin 1000 mg/d (Figure 16). Among prior nonresponders to interferon/ribavirin re-treated with peginterferon alfa-2b 1.5 µg/kg plus ribavirin 1000 to 1200 mg/d for 12 weeks, followed by peginterferon alfa-2b 1.0 µg/kg plus ribavirin 800 mg/d for 36 weeks, Lawitz reports an SVR rate of 9% (EJ Lawitz, personal communication; November, 2002) similar to that reported by Jacobson et al in prior nonresponders re-treated with peginterferon alfa-2b 1.5 µg/kg plus ribavirin 1000 to 1200 mg/d for 12 weeks, then peginterferon alfa-2b 1.0 µg/kg plus ribavirin 800 mg/day for 36 weeks. An important feature of this study is the finding that prior nonresponders with a >1-log drop in HCV RNA with their initial course of treatment have a significantly better chance of response to peginterferon plus ribavirin than those with a decrease of <1 log. The same SVR rate of 9% was reported by Freilich et al among prior nonresponders re-treated with peginterferon alfa-2b 1.0 µg/kg plus ribavirin 800 mg/d plus amantadine. A similar rate, 11%, was reported by Shiffman in nonresponders re-treated with peginterferon alfa-2a 180 µg plus ribavirin 1000 to 1200 mg/d. In a

![Figure 15. Virologic Response in Previous Combination Therapy Nonresponders: Nongenotype 1+](image-url)

![Figure 16. Peginterferon alfa-2b/Ribavirin SVR in Previous Nonresponders and Relapsers](image-url)
number of studies, relapers to prior therapy have shown higher SVR rates than nonresponders upon retreatment with various peginterferon-based therapeutic regimens (38%-68%).

Higher doses of peginterferon/ribavirin may further improve outcomes in interferon/ribavirin nonresponders. The RENEW trial is comparing peginterferon alfa-2b 0.5, 1.5, and 3.0 µg/kg QW, in combination with ribavirin 12 to 15 mg/kg/d. The rationale for this study arose from a retrospective analysis of data from peginterferon alfa-2b/ribavirin trials in treatment-naïve patients that suggested a dose-response effect for both interferon and ribavirin. The low-dose arm was closed when the FDA approved the 1.5 µg/kg dose as standard treatment for treatment-naïve patients. Early data reported by Gross et al show 24-week response rates of 53% for the 3.0 µg/kg peginterferon treatment arm compared with 39% for the 1.5 µg/kg arm.

**Conclusion**

This case study shows the potential virologic benefit offered by retreatment to patients who have not responded to or have relapsed following prior therapy. The occasional interferon monotherapy nonresponder who has never received ribavirin should be re-treated with peginterferon, rather than interferon, plus ribavirin, despite the absence of comparative data. Combination therapy relapers should be offered a course of peginterferon/ribavirin, based on the results of promising retreatment data. Most importantly, nonresponders to prior interferon/ribavirin combination therapy also can be offered a course in peginterferon/ribavirin, particularly those with more advanced fibrosis and/or a major drop in viral load (i.e., >1-log drop) with prior therapy. Patients must be advised, however, that data thus far suggest a low probability of SVR, and individualized decisions are required regarding duration of therapy. More than 48 weeks of treatment may be necessary in those patients who have been fortunate to achieve a response on treatment, but this remains speculative pending a clinical trial of 18 to 24 months of therapy for this population. A higher dose of peginterferon may also be necessary, but this also remains speculative pending final results of the RENEW trial.

**Final Thoughts**

The focus of this Tx Reporter has been presentation of the most recent data regarding treatment of HCV infection, comparison of the available pegylated interferon products, and management of HCV infection in hard-to-treat patients. The clinical benefits of pegylated interferons are now beyond question. The issue is no longer whether they represent a new standard of care. It is widely accepted that indeed they are the new standard of care, due to their increased efficacy and convenience. Rather, the current issue is how do clinicians use them optimally to effect sustained response in as many patients as possible, including hard-to-treat patients, and prior nonresponders and relapers. With two pegylated interferon products now approved, the differences between them must be examined and prescribing clinicians must determine the relevance of their differences in terms of clearance, half-lives, and stability of products.

Much new data is available regarding evaluation of EVR at 12 weeks in patients receiving peginterferon plus ribavirin combination therapy. It is clear that, in the absence of a ≥2-log drop of HCV RNA at 12 weeks, it is unlikely a patient will achieve an SVR. What is not clear, however, is what benefit, particularly in terms of histologic improvement, is gained by continuing both peginterferon and ribavirin without the hope of sustained response. Data emerging from ongoing clinical trials of maintenance therapy will help clarify the role of long-term treatment with peginterferon monotherapy beyond viral eradication, to the prevention of progression to cirrhosis and the development of carcinoma.

Hard-to-treat patients include those with negative predictive factors, such as obesity, genotype 1 infection, high viral load, bridging fibrosis, age >40 years, male gender, and prior nonresponse or relapse. Strategies to individualize therapy for these patients will optimize their chances at SVR. These strategies include weight-based dosing; promotion of good adherence, which is particularly beneficial for genotype 1 infection; side-effect management, which allows completion of a full therapeutic regimen; evaluation of early response to make informed ongoing treatment decisions; and ongoing education and support of the patient. Patients with advanced liver disease receive histologic benefit from therapy in addition to the potential benefit of viral eradication. In the absence of viral eradication, however, the histologic benefit may still be facilitated through long-term maintenance therapy using peginterferon monotherapy. Final results from multiple major trials are pending.

Retreatment using peginterferon/ribavirin for patients who have not responded to or who have relapsed following prior standard interferon-based therapy provides these patients with another chance at viral eradication. The likelihood for response with retreatment is highest in patients who had a significant drop in viral load on prior therapy and in patients who relapsed. The antifibrotic activity and subsequent histologic benefit of peginterferon suggest that patients with advanced liver disease are candidates for retreatment, regardless of their likelihood for virologic response. Physicians who treat HCV infection are now equipped with greatly improved therapies, as well as effective management strategies to optimize their efficacy. With these therapies and strategies, physicians can help the majority of their patients achieve sustained virologic, as well as histologic, response.
References


19. Algranati NE, Sy S, Modi M. A branched methoxy 40kda polyethylene glycol (PEG) moiety optimizes the pharmacokinetics (PK) of peginterferon alfa-2a (PEG-IFN) and may explain its enhanced efficacy in chronic hepatitis C (CHC). Hepatology. 1999;30:190A.


31. Modi MW, Fulton JS, Buckmann DK, Wright TL, Moore DJ. Clearance of pegylated (40kDa) interferon alfa-2a (PEGASYS®) is primarily hepatic [abstract 848]. Presented at: 51st Annual Meeting of AASLD; October 27-31, 2000; Dallas, Tex.
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To receive an acknowledgment of your participation for CME credit, please complete the following steps:
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Please select the most appropriate response to each question.

1. Qualitative HCV RNA testing is an appropriate assay by which to assess early virologic response (EVR).
   - True   - False

2. The slopes of both the first and second phases of viral decay following interferon administration correlate closely with SVR.
   - True   - False

3. The goals of assessing EVR are to minimize loss of continued therapy in potential sustained virologic responders and to maximize stopping of therapy in nonresponders.
   - True   - False

4. When using pegylated interferon/ribavirin combination therapy, EVR is defined as ≥2-log drop in HCV RNA or PCR negativity at 12 weeks.
   - True   - False

5. Patients who achieve EVR and are HCV RNA negative at 12 weeks should be retested at 24 weeks.
   - True   - False

6. The principle of stopping therapy based on EVR assumes that SVR is the only beneficial endpoint of treatment.
   - True   - False

7. Peginterferon alfa-2a and peginterferon alfa-2b are both approved by the US Food and Drug Administration (FDA) for the treatment of hepatitis C.
   - True   - False
8. Although viral kinetic studies have demonstrated that maximum suppression of HCV replication is maintained during the traditional 48- to 72-hour dosing cycle of standard interferons, viral re-emergence may occur during the nadir period.
   ❑ True    ❑ False

9. Both peginterferon alfa-2a and peginterferon alfa-2b have demonstrated a twofold increase in the rate of SVR compared with nonpegylated interferon.
   ❑ True    ❑ False

10. Peginterferon alfa-2a is a flat-dosed product, whereas peginterferon alfa-2b is weight-based dosed.
    ❑ True    ❑ False

11. Pegylation is expected to result in an increase of specific bioactivity of protein pharmaceuticals relative to their nonpegylated counterparts.
    ❑ True    ❑ False

12. The specific activity of a pegylated molecule in vitro has been shown to correlate directly with its clinical efficacy in vivo.
    ❑ True    ❑ False

13. The phase 3 clinical trials of peginterferon alfa-2a and peginterferon alfa-2b in combination with ribavirin were both powered to statistically address the effectiveness of the drug specifically in the subgroup of patients with genotype 1 infection and high viral load.
    ❑ True    ❑ False

14. The difference between a patient’s degree of HCV RNA level reduction and the 2-log EVR threshold should be assessed in terms of the assay’s acceptable degree of error, which is typically considered to be within about a half-log.
    ❑ True    ❑ False

15. Adherence affects SVR equally among all genotype groups.
    ❑ True    ❑ False

16. Body surface area has been shown to be a significant predictive factor for SVR with weight-based dosed peginterferon alfa-2b.
    ❑ True    ❑ False

17. Yano et al demonstrated that approximately 35% of patients who initially presented with stage 2.0 to 2.9 liver disease progressed to cirrhosis within 5 years.
    ❑ True    ❑ False

18. In a study that retrospectively reviewed pooled data from 3010 patients, Poynard et al found that the majority of patients who showed reversal of cirrhosis were also sustained responders.
    ❑ True    ❑ False

19. In patients who do not achieve virologic response with primary therapy, a long-term course of pegylated interferon monotherapy (maintenance therapy) may retard the progression of liver disease or even improve fibrosis.
    ❑ True    ❑ False

20. Retreatment data are promising, showing that prior nonresponders and relapers to standard interferon-based therapies have equivalent probabilities of achieving SVR with peginterferon/ribavirin combination therapy.
    ❑ True    ❑ False

Thank you for your participation.
Instructions

Please complete this survey, along with the CME Posttest, and mail or fax (both sides) to Projects In Knowledge, One Harmon Plaza, Secaucus, NJ 07094; fax: 201–617–7333.

1. Please rate the extent to which you achieved the learning objectives:

   • Describe the efficacy and safety implications of the pharmacodynamic and pharmacokinetic properties of pegylated interferons.
   - [ ] Excellent  [ ] Very Good  [ ] Good  [ ] Satisfactory  [ ] Poor

   • Discuss new data regarding the effect of weight-based dosing of ribavirin and treatment duration on treatment safety and efficacy.
   - [ ] Excellent  [ ] Very Good  [ ] Good  [ ] Satisfactory  [ ] Poor

   • Evaluate the potential of early HCV RNA levels to predict response or nonresponse and the usefulness of such predictions in making early treatment-stopping decisions.
   - [ ] Excellent  [ ] Very Good  [ ] Good  [ ] Satisfactory  [ ] Poor

   • Prescribe peginterferon/ribavirin combination therapy for all patient groups, including patients with multiple challenges.
   - [ ] Excellent  [ ] Very Good  [ ] Good  [ ] Satisfactory  [ ] Poor

   • Relate the histologic benefit of peginterferon/ribavirin combination therapy to the need of patients with fibrosis, including those with cirrhosis.
   - [ ] Excellent  [ ] Very Good  [ ] Good  [ ] Satisfactory  [ ] Poor

2. Please rate the educational value of this material:

   - [ ] Strongly Agree  [ ] Agree  [ ] Disagree  [ ] Strongly Disagree

3. Course was free from commercial bias:

   If you “Disagree” or “Strongly Disagree,” why?

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   - [ ] Just Right  [ ] Too Advanced  [ ] Too Basic

4. Please rate the level of the material presented:

   - [ ] Excellent  [ ] Good  [ ] Satisfactory  [ ] Poor

5. Please list any changes in your practice that you would consider making as a result of participating in this activity:

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<td>e. Multimedia (online, CD-ROM)</td>
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</table>

7. Please tell us how long it took you to complete this course: ................................................................. ..................................................................

8. Please list topics and/or experts you would find interesting and professionally relevant for future CME activities:

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9. Follow-up

As part of our ongoing continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our CME courses on professional practice. Please indicate your willingness to participate in such a survey.

☐ Yes, I would be interested in participating in a follow-up survey.

☐ No, I’m not interested in participating in a follow-up survey.

Additional comments about this activity:

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Thank you for your participation.